Mastering AVI

part 1: Introduction to regulatory landscape of visual inspection

- USP 1, USP 788 and 1788, USP 790 and 1790
- PhEur e.g. 2.9.20
- JP e.g. 6.06
- Annex 1
- Similarities and differences in compendial methods
- 100% inspection and AQL testing
- Definitions and practical examples of inherent, intrinsic and extrinsic particles
- Examples of regulatory citations 483s
- Recall recaps

PDA Parenteral Drug Association

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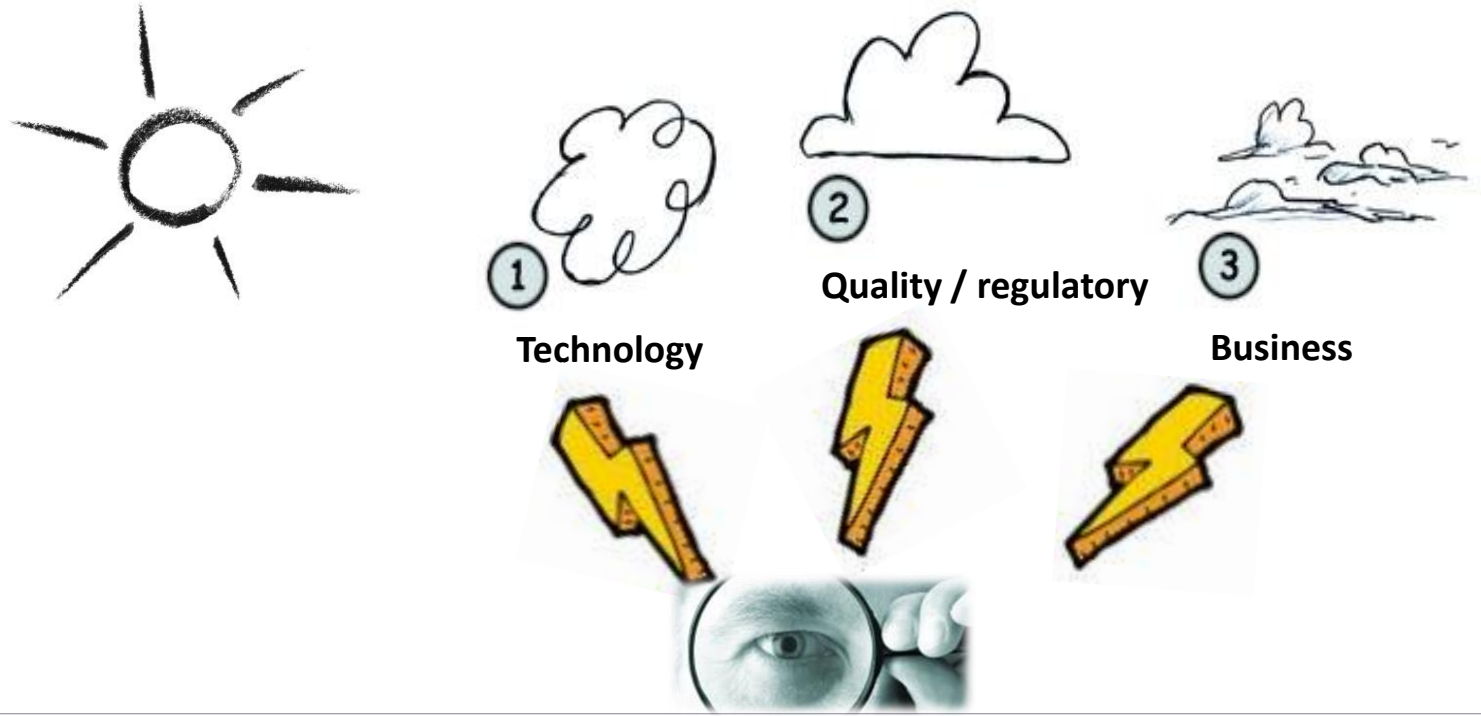
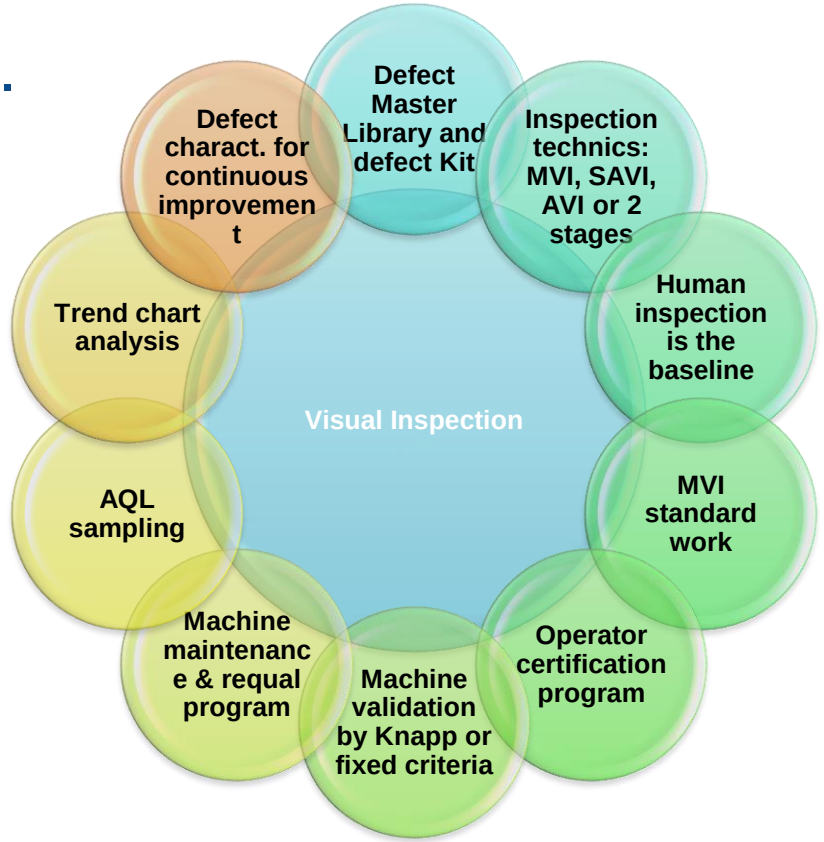
Introduction to regulatory landscape of visual inspection



10 Golden rules for VI…..



Compendias

- USP<1>
- USP<788> particle definition
- **USP<790>**
- **USP<1790> revision may 2022 +20pages = expectations of FDA**
- **USP<1207> concerning Leak Testing**
- **PhEur e.g. 2.9.20 vis**
- JP e.g. 6.06
- **Annex 1: in place in Aug 2023**
- **New FDA guidance on Particle draft dec 2021**
- Similarities and differences in compendial methods
- 100% inspection and AQL testing
- Definitions and practical examples of **inherent, intrinsic and extrinsic particles**

Compendias

- USP<1790> Effective May 2022 rev 3

Microsoft Edge
PDF Document

- Particle guidance FDA (draft)

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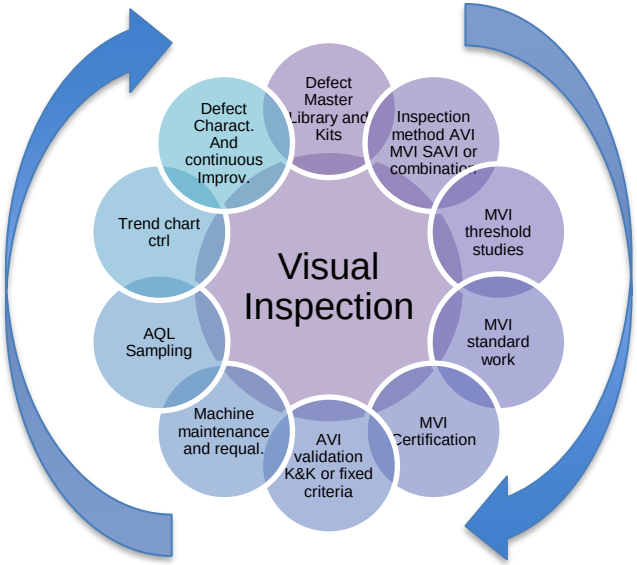
PDF Document

- New Annex 1 Effective Aug 2023

Microsoft Edge
PDF Document

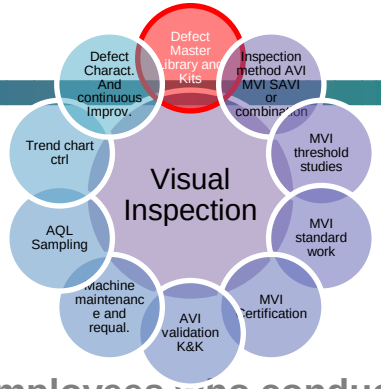
Inspection trends with Recent FD 483s

Learning from errors and FDA citation



Note: the findings statements reported after are excerpts of a list released under the Freedom of Information Act and published by the FDA on FDA website. Those findings are anonymized.

Defect kits



2009

« There is **no standardized kit of defects for the training** of employees who conduct visual inspection of the vials components “

2013

“Your operator's visual inspection of Lyophilized drug product qualification program **does not include examples of glass particulate in vials for training purposes**.”

2014

“The defect sets utilized for qualification of inspection **do not have defects that are representative of defects found in routine inspection**, **retention examination, and complaints**”

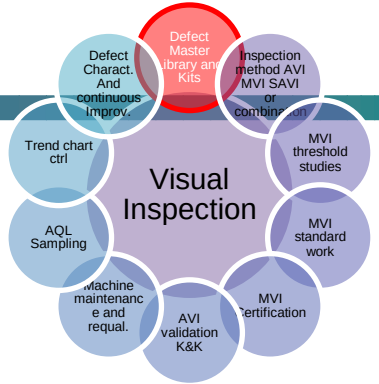
2018

“There are no documented procedures or reference for the creation of the visual inspectors qualification kits. ….. There are no established specifications for the size of the particle included with the kits”

USP<1790>

- 7.1 Standards
- 7.2 Preparing Defect Standards
- 7.3 Particle Types

Test sets



2016

« Qualification of visual inspectors and validation and verification of the **….inspection system are not based on well-characterized test sets. No written procedure has been established to ensure test sets** for visual inspection include particles in the visible size range similar to production rejects other than a …..micron glass particle.
No record documenting the creation of test sets used for qualification of visual inspectors was provided….”

2017

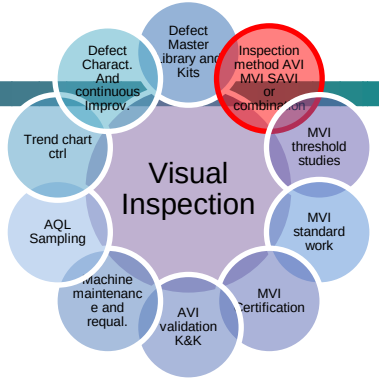
“Defects that typically occur during production **are not characterized in sufficient detail** to allow for consistent creation or selection of defects to include in test sets used for qualification of inspectors. Additionally, during creation of defect test sets, **defects in the test sets are not well-characterized to ensure they are representative of typical production defects. For example, there is no information on particle size, particle material type (for light and dark particles), crack size, and crack location.”**

2022

Your firm did not evaluate extrinsic particulate, such as hair, detectability during

USP<1790>
- 7.1 Standards
- 7.2 Preparing Defect Standards
- 7.3 Particle Types

Multiple stage inspection



2015

« Lots of finished drug product that fail the initial automated visual inspection limit on the system can then be re-inspected using the semi-automated manual system .**There are no establish limits for the re-inspection of lots of product that fail the initial inspection that are then re-inspected..**.”

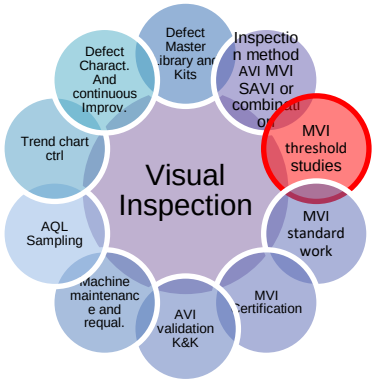
2018

“You have not adequately assessed **spinning parameters, such as rotation per minute (RPMs) of your semi-automated inspection** equipment which affect the capability of your visual inspection process.”

USP<1790>

- **3. TYPICAL INSPECTION PROCESS FLOW**
- **3.3 Remediation and Alternative Practices- two stage inspection**
- **6.2 Semi-Automated Visual Inspection**

MVI Baseline performance studies



2017

"The probability of detection of particulates used in the defect test sets for manual visual inspection has not been determined to qualify these defects for use in the test set."

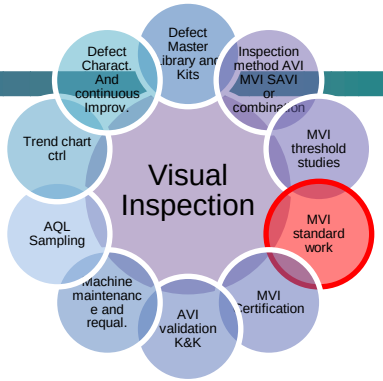
2022

Your firm does not have a program to re-evaluate performance qualifications based on continued process improvements. For example, your firm has implemented a test case for gray zone evaluation for new recipe performance qualifications. Your firm also now performs confidence interval calculations for acceptance criteria of Machine Comparison to Manual Inspection Baseline. These recently implemented test cases have not been retroactively applied to previously qualified recipes to assure they are still in a qualified state.

USP<1790>

- 7.4 Rejection Probability Determination
- 7.6 Types of Test Sets – Threshold studies

Standard work MVI



2011

« The visual inspection certification program is not adequate : ….., no rotation of the unit required during the visual inspection..”

2016

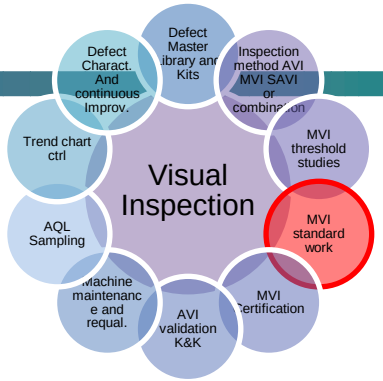
“During the visual examination, I observed that the operator's visual inspection process was inconsistent in the amount of inspection time she spent on drug product units.”

“SOP … does not instruct the visual inspector to gently swirl and invert the container during visual inspection”

USP<1790>

- 6.1 Manual Visual Inspection – critical process parameters in MVI

Standard work MVI



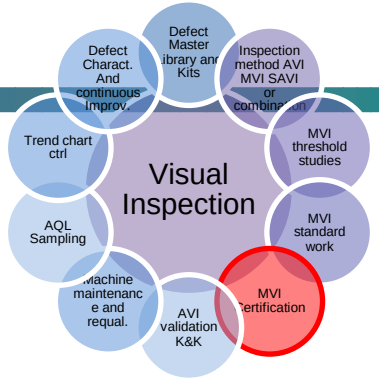
2022

fiber was observed during the retain review prior to being dislodged. The inspection procedure for syringes was not reviewed or retraining did not take place to ensure visual inspection would capture this defect in the future.

USP<1790>

- 6.1 Manual Visual Inspection – critical process parameters in MVI

Certification conditions



2011

"procedures and current practices for the certification of the operators conducting visual inspection were found not representative of current production conditions »

2012

« ..The qualification does not entail reviewing and identifying defects under the same conditions that during manufacturing operations "

2016

"The certification exercise does not simulate conditions observed during routine product inspection operations ……..Therefore, the current certification/re-certification procedure does not challenge the capability of the operators to recognize and separate all types of defective vials during the maximum individual inspection interval "

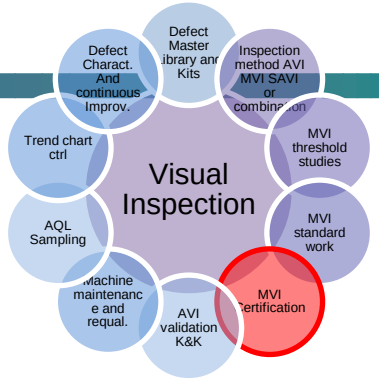
2022

You cannot confirm through documentation the inspection times during the execution of visual inspection qualification tests is representative of routine visual inspections.

USP<1790>

- 7.7 Training and qualification of human inspectors

Certification conditions



2017

“Routine visual inspection occurs on-line with operators ….. During the qualification the operators work offline …”

2018

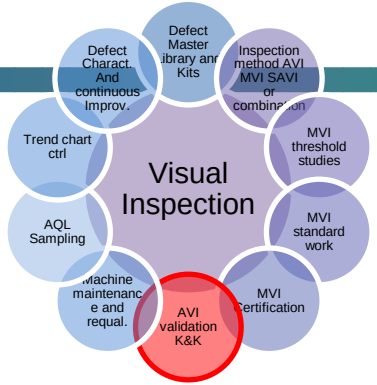
“however these photographs are unclear and inadequate to identify glass particles in vials. Without an adequate qualification vial, your firm cannot ensure your operators can observe this defect during I00% visual inspection.

…. your firm does not have a procedure to address an employee who repeatedly failed to identify a specific defects during all operator qualification runs”

USP<1790>

- 7.7 Training and qualification of human inspectors

AVI Validation



2014

"….**Data was not available** at the time of the inspection to demonstrate that the ….. **has been qualified as equal to or better** than the ….. inspection..."

2017

« ….. There is no documentation of Process Qualification study of the … **machines capabilities to detect vials heel crack defects**."

2022

Your firm did not demonstrate that the Automated Inspection Machine is better than or equivalent to manual inspection

USP<1790>

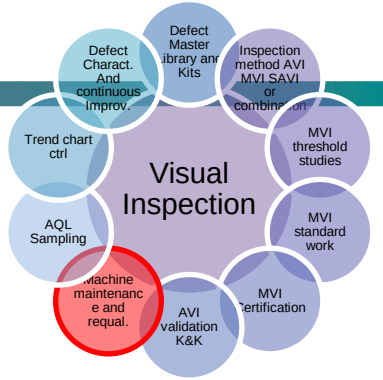
9. Conclusion –

……Where machine methods are used, the equipment must be validated to demonstrate equivalent or better performance when compared to manual inspection.

6.3 Automated Visual Inspection

……Significant effort is required to program these systems and to test their performance against a range of known defects,

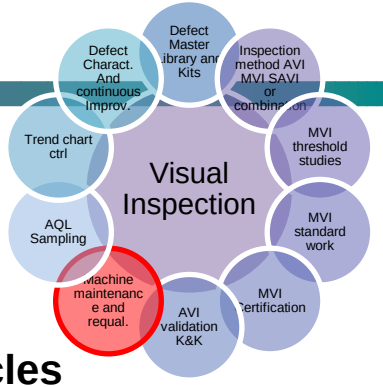
Machine Maintenance / Daily test



2014
"Vials could be heard hitting against each other during the addition... This practice potentially subjects post visually inspected vials to damage. "
2015
« **The light intensity of each unit is not verified during routine preventive maintenance** and is not verified prior to use. …….
The functionality test used to determine the reject function of the equipment is required before and after 100% visual inspection.
The functionality test results for each equipment is not clearly documented as to the test results. …. „
2015
"The …. equipment are used to perform 100% visual inspection of lyophilized vials, …... For example,…. **The light intensity of each unit is not verified during routine preventive maintenance** and is not verified prior to use. "

Annex1
8,31 routine check

Machine Maintenance / Daily test



2022 efficiency of operating parameters to resuspend particles

reasons such as being stuck in the stopper or on the vial wall. The AIM qualification documents also did not demonstrate that the machines inspection method could resuspend the particulates in the product once they became undetectable/stuck on the vial wall.

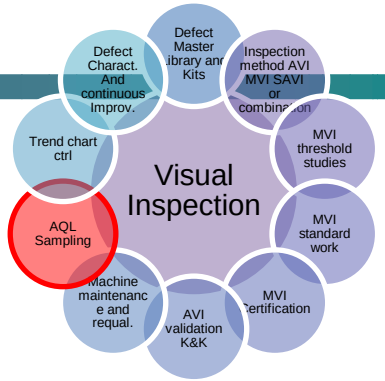
2022 daily check

Routine checking of equipment is not performed -according to a written program designed to assure proper performance. Specifically,

Your firm does not assure that the Automated Inspection Machine is working within expected parameters during set up for a run. Your firm uses a challenge set with gross defects only prior to running in order to check machine operability. The challenge set does not include vials that are at a known visible range of detection. According to A-SOP-22-03-014, *Automated Vial Inspection*

Annex1
8,31 routine check

AQL QUALITY OVERSIGHT



2011

“There is no direct QA oversight of the operators performing the visual inspections. Operators are only observed during their certification process, but not on a routine basis.”

2015

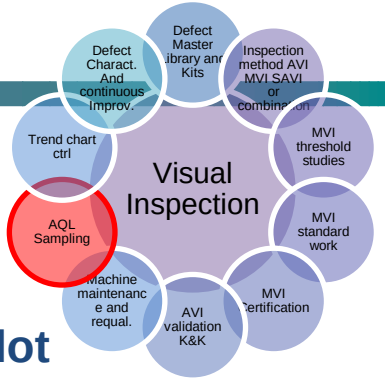
« Quality oversight over visual inspection is deficient. For example,

a. AQL inspections are conducted by personnel that also perform the 100% visual inspection

b. From September 2013 to September 2015, **QA oversight over the 100% visual inspection operations has occurred six times**.”

USP<1790>
3. TYPICAL INSPECTION PROCESS FLOW
3.1 100% Inspection
3.2 Acceptance Sampling and Testing

- Inspection trends for VI with some recent FD 483s



Action after AQL failed

2015

« **There was no tightened 100% inspection performed for this lot even though the initial AQL failed for a Major defect.** “

2015

“There are no established limits for the number of times any single lot can be re-inspected. Additionally, there are no tightened limits established for the re-inspection”

2015

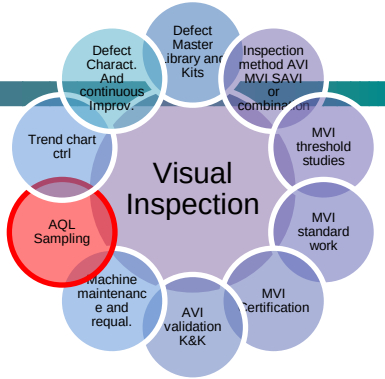
“there is **no requirement to tighten the inspection limits or increase the sample size** for the second AQL inspection”

2016

“reported a particle identified in a vial during an AQL inspection. There was no documentation on the identity of the particle and whether it was inherent or foreign (black debris, fiber, glass fragments, etc.).”

USP<1790>
3. TYPICAL INSPECTION PROCESS FLOW
3.1 100% Inspection
3.2 Acceptance Sampling and Testing

- Inspection trends for VI with some recent FD 483s

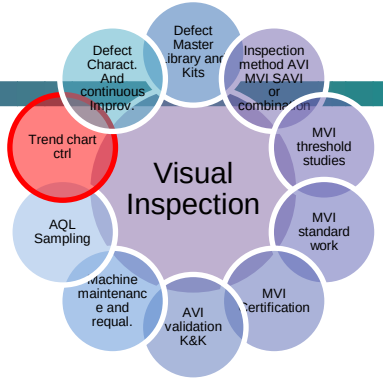


AQL sampling on entire batch

2022

Your firm does not take AQL samples that are reflective of the entire batch. Your firm has had approximately [redacted] drug products which exceeded AQL limits during visual inspection [redacted] It is in your procedure, A-SOP-03-04-001, to segregate product that has exceeded AQL at the time of inspection and reinspect the segregated portion under a tightened inspection. The remaining, uninspected, portion is then continued to be visually inspected under normal AQL inspection levels with a new batch size created. AQL inspection is performed while visual inspection is in progress, however, there is no documentation for when AQL samples are inspected. There is also no documentation for which skids have been sampled. According to the AQL procedure, the samples should represent "good saturation" throughout the batch, however this is not verifiable based on current AQL documentation. Segregation of the AQL portion that exceeded limits relies on immediate action from the QA inspector to hold and segregate those AQL portions.

Trending



2011

« There is no written SOP that include performing trend evaluation to determine the root cause that created the quality related attributes”

2013

“There is no tracking or trending of the number of xx vials initially rejected as “Particulate Fiber” ”

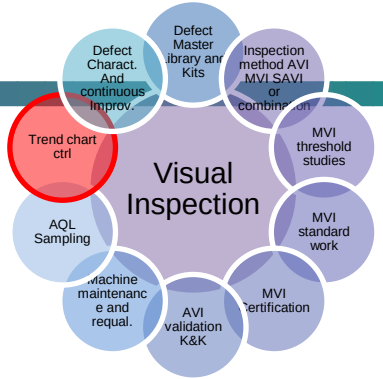
2016

“inspection system, does not have an overall alert/action limit for total rejections”

2018

“You do not monitor long term drift during your establishment / re-establishment of in-process limits.”

Trending



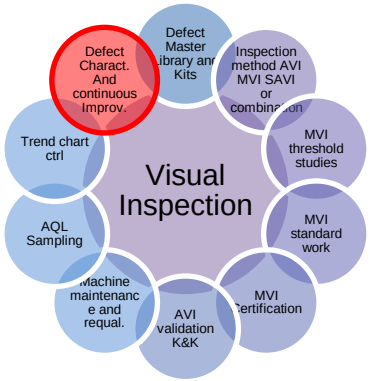
2022

H. Your firm does not document the identity of particulates found during visual inspection of aseptically filled product. All particulates identified by the Automatic Inspection Machine (AIM) are grouped into a single category regardless of whether it is intrinsic or extrinsic particles. During manual inspection, all intrinsic particles are grouped together and are not categorized as glass, fiber, colored particle, etc. This is significant as no trending can be performed on the particulates without sub-classification and complaints, or other investigations are hampered due to lack of information documented in the batch records.

ANNEX1 8,29
defect types should be categorized and batch performance analyzed. Batches with unusual levels of defects, when compared with routine defect numbers for the process (based on historical and trend 1062 data), should lead to an investigation.

Annex1
8,29 defect trends

Continuous improvement



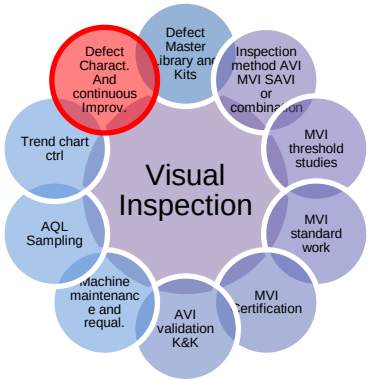
2015

« According to SOP …., the test set library shall be largely covered with regards to existing (i.e., known) defects. No less than eight deviations for cracks on vial bottoms occurred since approximately ….., for example, deviation …... This defect type has not been added to the test set library to date”

2015

“Particles size was not determined to facilitate assessment of the reliability of detection during visual inspection”

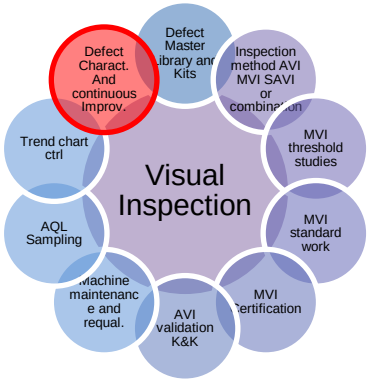
Continuous improvement



2022

The following lots exceeded internal control limit for various categories of visual defects such as Major A defect, defined as Fibers or Intrinsic Particulate (Elongated undissolved matter or particulate matter originating from a normal manufacturing process that is floating freely within the product or that is attached to the product contact area of the stopper), or Major B defect, defined as non-conformities that could lead to serious impairments of the container or potential impact to product quality. Investigation into these limit breaches to determine potential root causes did not occur as appropriate.

Complaint particle identification



2022

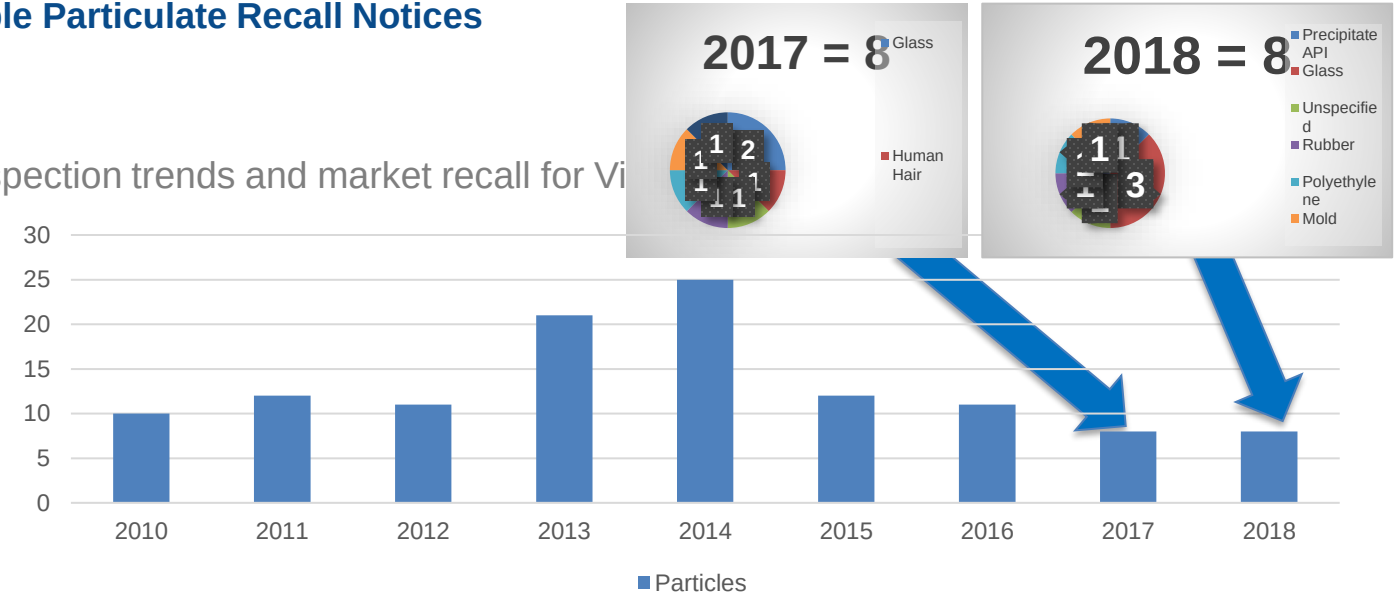
B. As provided by your firm, [redacted] supplier complaints for stopper related issues were submitted [redacted]. Out of these, [redacted] supplier complaints were related to Stopper [redacted]. [redacted] investigations are still open [redacted]

Your firm did not perform an adequate investigation into the repeat stopper defect reported. Your investigation of the [redacted] supplier complaints related to stopper [redacted] relied in large part on the supplier investigation. For the [redacted] SCR, the supplier investigations concluded that that stopper [redacted] either "met agreed qualification" or "a root cause cannot be determined".

Market recall trends for Visual Inspection

VI Recall trends for US Market
Visible Particulate Recall Notices

- Inspection trends and market recall for Vi



Prepared by John Shabushnig, Insight Pharma Consulting from Recall Archive data on fda.gov

Many thanks to contributors
- John Shabushnig for FDA recall analysis

Thank you for your attention
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